Journal of Clinical Oncology

The Official Journal of the American Society of Clinical Oncology

Vol 21, No 13 **July 1, 2003**

EDITORIAL

Maintenance Therapy in Advanced Ovarian Cancer: Progression-Free Survival and Clinical Benefit

MOST PATIENTS with advanced ovarian cancer achieve a clinical complete remission after cytoreductive surgery and combination chemotherapy, usually with six cycles of taxane (in most cases paclitaxel) together with carboplatin. Unfortunately, the majority of patients experience disease recurrence. Although second-line treatments provide effective palliation and may extend survival, they are not curative. Consequently, an effective consolidation or maintenance therapy that would prevent recurrences after a clinical complete response could have a potentially greater impact in advanced ovarian cancer than in other common epithelial tumors, in which only a minority of patients achieve a clinical complete remission with induction chemotherapy. Both consolidation therapy and maintenance therapy in ovarian cancer patients who achieve a clinical complete remission have been studied in a series of clinical trials. Consolidation therapies have focused on relatively short-term treatments that include high-dose chemotherapy with a stem-cell transplant,[1,2] whole abdominal radiation therapy,[3,4] or intraperitoneal administration of p32 or antibodies conjugated with a variety of radioisotopes.[5,6] Maintenance therapies have focused on prolonged administration of single-agent chemotherapy,[7,8] extended cycles of induction chemotherapy,[9-11] intraperitoneal chemotherapy,[12] hormonal therapy,[13] and immunotherapy, including interferon[14] and vaccines targeting CA-125.[15,16] Neither consolidation therapy nor maintenance therapy has been shown to extend survival in patients with advanced ovarian cancer, although only a few randomized controlled trials with sufficient power to detect relevant clinical differences have been reported.

In contrast to these previous reports (although some studies are still in progress), the report by Markman et al[17] in this issue of the *Journal of Clinical Oncology* demonstrates that 12 cycles of intravenous paclitaxel administered every 28 days to women in a clinical complete remission resulted in a 7-month improvement in median progression-free survival, compared with those who received three cycles of paclitaxel. The Data Safety Monitoring Committee for this trial recommended discontinuation of the trial at a time when there was a statistically significant improvement in time to progression, but no difference in overall survival, between the treatment arms. It is unlikely that any survival advantage (if such an advantage truly exists) will be detected, because accrual was stopped, and patients assigned to three cycles of therapy were permitted the option of receiving an additional nine cycles of treatment.

Major questions from this study are unanswered: Is there sufficient clinical benefit associated with a 7-month improvement in progression-free survival resulting from an additional 9 months of chemotherapy? Should maintenance paclitaxel be considered a potential new standard of treatment? An improvement in progression-free survival seems intrinsically desirable; however, by itself, it does not establish clinical benefit, which requires either an improvement in survival or an improvement in quality-adjusted survival. Consequently, the toxicity of maintenance therapy needs to be emphasized. Patients eligible for this study were excluded if they had at least grade 2 neuropathy from prior therapy. Despite this important exclusion criterion, significant neuropathy developed in patients randomly assigned to the 12-cycle arm: 23% of patients developed grade 2 or 3 neuropathy and 7.5% of patients discontinued therapy because of neuropathy. When coupled with prolonged alopecia, myalgias, and fatigue, the cumulative toxicity of 12 months of treatment is substantial. Unfortunately, a formal quality-of-life assessment was not included in this protocol, and progression-free survival may not be as clinically significant to a patient as symptom-free survival. Patients were monitored on a monthly basis in this study and it is unclear how often patients were judged to have clinical progression on the basis of an increasing CA-125 or on physical evidence of disease progression, without any associated symptoms.

Concerns about toxicity would be lessened if it had been shown that overall survival was improved with maintenance therapy; an increase in progression-free survival alone cannot be considered a surrogate for improvement in overall survival. The demonstration that the hazard for disease progression markedly increased after maintenance therapy was stopped after either 3 or 12 months of treatment indicates that residual disease was present in many patients despite maintenance therapy, and that

long-term survival would not be improved. Consequently, although this study does not establish clinical benefit for 12 months of maintenance paclitaxel, it does demonstrate that additional therapy has a biologic and clinical effect on delaying disease progression. Additional studies will be necessary to determine whether this observation can be developed into a strategy in which clinical benefit is established for patients who achieve a clinical complete remission with induction chemotherapy.

The results of this study must also be placed in context with previous clinical trials in ovarian cancer that have failed to demonstrate an improvement in survival for patients receiving any form of maintenance or consolidation therapy. It also must be emphasized that maintenance therapy has been studied in other solid tumors, including germ cell tumor of the testes, lymphomas, and breast cancer, without any demonstration of an improvement in survival. Studies of maintenance therapy in breast cancer perhaps have the greatest relevance to interpretation of the results of the present study. Muss et al[18] reported on 250 women with metastatic breast cancer who were treated with combination chemotherapy, and responding patients or patients with stable disease were randomly assigned to maintenance therapy or observation. Maintenance chemotherapy led to a 6-month prolongation of progression-free survival without any difference in overall survival. Coates et al[19] randomly assigned women with metastatic breast cancer to continuous versus three cycles of chemotherapy, with treatment reinstituted at the time of disease progression. Once again, the two groups had equivalent survival. However, the group receiving three cycles had a lower response rate, shorter time to progression, and a decrement in quality of life. Consequently, it has been postulated that five to six cycles of treatment, which is the number of cycles of combination chemotherapy patients received before receiving maintenance therapy in the study by Markman et al,[17] could maximize the response to chemotherapy, and perhaps improve quality of life.[17]

The standard of care in asymptomatic metastatic breast cancer is to treat patients with intensive induction chemotherapy to achieve a maximum response. Because there is no evidence that continuing treatment has an effect on overall survival, chemotherapy can be discontinued and readministered at the time of disease progression.[20] Conversely, in a patient with symptomatic metastatic breast cancer who achieves excellent palliation with chemotherapy associated with acceptable toxicity, chemotherapy can be continued with a goal of delaying the subsequent disease progression, and this may be associated with an improvement in quality of life. In the study by Markman et al,[17] because patients in a clinical complete remission were already asymptomatic, there is no clinical benefit of maintenance therapy in preventing and delaying symptomatic disease progression.

In the context of previous trials in solid tumors that have failed to demonstrate an effect of maintenance therapy on survival, one needs to consider the question of what the likely outcome would have been if the primary end point of this study had been survival, and the study had been continued despite the emergence of a statistically significant difference in progression-free survival. If the 7-month improvement in progression-free survival were also associated with a clinically significant improvement in overall survival, this would be the first demonstration that maintenance therapy improves survival, on the basis of the possibility that there are unique biologic characteristics of ovarian cancer. However, molecular profiling of ovarian cancer has not identified any factors that would uniquely make ovarian cancer (in contrast to other common solid tumors) a disease for which maintenance chemotherapy leads to an improvement in survival. In addition, the hazard ratio for progression increased after completion of maintenance therapy, indicating that patients still had residual disease despite the prolonged chemotherapy. Even if the study had not been stopped, it seems unlikely, but not impossible, that maintenance therapy would have improved survival compared to a strategy of reinstituting effective therapy at the time of disease progression after initial achievement of a clinical complete remission.

On the basis of the results of this trial, patients and their physicians will likely consider maintenance therapy as an option. Without establishing true clinical benefit, it cannot be considered a new standard of care, as the authors themselves conclude. The Gynecologic Cancer Intergroup, which consists of clinical researchers throughout the world who are conducting prospective randomized trials of new chemotherapy regimens, have reviewed the results of this study and no protocols were changed to incorporate maintenance therapy. For example, Gynecologic Oncology Group trial 182, a five-arm randomized trial currently comparing treatment with paclitaxel plus carboplatin to four experimental regimens (which include agents such as encapsulated doxorubicin, gemcitabine, and topotecan), does not permit maintenance therapy. If there were consensus that maintenance therapy with monthly paclitaxel is appropriate for all patients with advanced ovarian cancer in a clinical complete remission, Gynecologic Oncology Group trial 182 would have required modification. Furthermore, additional European clinical trials that are evaluating maintenance chemotherapy (either in the form of paclitaxel or topotecan) in which patients on the control arm receive no treatment after induction chemotherapy, and in which survival is the primary end point, are still in progress.

Markman et al[17] also emphasize the need for additional trials to determine if there are clinical benefits from maintenance chemotherapy, which would incorporate quality-of-life, symptom-control, and survival factors. However, the results of their study, coupled with extensive prior experience in other solid tumors, indicate that maintenance with traditional chemotherapy is unlikely to improve overall survival. It is possible that gene expression arrays may identify subsets of patients with advanced ovarian cancer in whom chemotherapy or molecular-targeted therapies may prove to be an effective maintenance strategy, and trials should evaluate such molecular correlates. Prospective randomized trials of maintenance strategies should also incorporate formal quality-of-life assessments. Until the completion of additional trials, the results of the study by Markman et al[17] should not routinely be used to recommend maintenance paclitaxel in patients with advanced ovarian cancer who have achieved a complete remission with standard induction chemotherapy.

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